Remarks/Arguments

A. Summary Of the Claims

Claims 6 and 9 were pending at the time the Action was mailed. Claims 1-5, 7-8 and 10-34 were previously cancelled. Claim 9 is cancelled herein, claim 6 is amended and claim 35 is new. Support for the amendment and new claim can be found throughout the specification and claims as originally filed. For instance, the subject matter of previous claim 9 has been incorporated into claim 6, and the phrase "perceived as causing teratogenicity" finds support in the specification as filed at, for example, paragraphs [0010]-[0015] (paragraph [0012] in particular), as well as paragraph [0020]. New claim 35 is directed to a combination of a pharmaceutical tablet and a graphical representation of a pregnant woman applied to the tablet surface and being visible to the naked eye. Support for new claim 35 is found, for example, at paragraphs [0022]-[0027] of the specification as filed.

Claims 6 and 35 are pending.

B. The Indefiniteness Rejection Is Overcome

Claims 6 and 9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner contends that the expressions "at least one active ingredient" and "comprises" render the claims confusing.

Applicant respectfully disagrees. The claims, prior to any amendment, were definite and satisfied the requirements under § 112, second paragraph. However, in an effort to further prosecution and secure prompt allowance in this case, the claims have been amended to address the Examiner's concern. As indicated above, claim 9 is cancelled. Claim 6 now recites that the pharmaceutical tablet comprises "a therapeutically effective amount of doxylamine succinate as an active ingredient perceived as causing teratogenicity and a therapeutically effective amount of

pyridoxine hydrochloride as another active ingredient...." Claim 35 also contains this language. As the claims no longer recite the phrases of concern, the indefiniteness rejection is moot.

C. The "graphical representation of a pregnant woman" Is A Proper Claim Limitation That Must Be Given Patentable Weight

The Examiner asserts that "[t]he picture is immaterial to the tablet composition [and] does not further limit nor provide patentable weight to the tablet composition" in the context of the indefiniteness rejection. Action, page 2. While the Examiner's reference to the "picture" was to the previously claimed "pregnancy-friendly indicia", Applicant presumes that the Examiner would apply this assertion to the presently claimed "graphical representation of a pregnant woman." However, this assertion is legally incorrect for at least the following three reasons.

First, the MPEP indicates that "all words in a claim must be considered" when assessing patentability. MPEP § 2143.03. While this section of the MPEP discusses this concept in the context of an obviousness analysis, the importance of words in claims has been emphasized by courts in other contexts as well. *See, e.g.*, *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996) ("[W]e look to the words of the claims themselves... to define the scope of the patented invention."); *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006) (as claims both define claimed subject matter and provide a notice function, "[C]laims are interpreted with an eye toward giving effect to all terms in the claim.") Thus, the Examiner's dismissal of the patentable weight of the claimed picture (that is, a graphical representation of a pregnant woman) is improper.

Second, the "graphical representation of a pregnant woman" that is applied to the surface of the claimed pharmaceutical tablet is a proper limitation of the claim. As noted in the

specification, such a representation is representative of "pregnancy-friendly indicia" that is "apt to be easily recognized as indicative of a safe medication for taking during pregnancy." Page 7, paras. [0027]-[0029]. Thus, such a graphical representation correlates to an indication of safety with respect to a medication. This element of safety is, necessarily, a limiting aspect of the claim. As such, the graphic is material and provides patentable weight to the claimed tablet.

Third, case law clearly indicates that an image that is part of a product may be accorded patentable weight. For example, in *United Systems of Arkansas, Inc. v. Laser Substrates, Inc.*, the Federal Circuit discussed an assignee's patent that claimed a post card assembly with an image placed on a single side of a form, and compared it to a competitor's form that had images on both sides. 31 Fed. Appx. 703 (Fed. Cir. 2002) (unpublished). The Federal Circuit discussed the prosecution history of the assignee's patent, noting that "Laser thus distinguished [its invention from the prior art] by emphasizing both the 'single pass' feature of the claimed invention ***and the content of the images*** that must be printed by that single pass." *Id.* at 708. Laser overcame the prior art by virtue of making both of these distinctions. *Id.* Thus, the images on Laser's claimed forms carried patentable weight, as their content was found to be patentably distinct from the images found in the prior art. Similarly, the graphical representation of a pregnant woman on the presently claimed tablets also carries patentable weight.

To the extent that any aspect of the indefiniteness rejection (or any other rejection) is based on the assertion that the presently claimed graphical representation of a pregnant woman fails to further limit the claims and does not carry patentable weight, the rejection cannot stand.

D. The Enablement Rejection Is Overcome

Claims 6 and 9 are rejected under 35 U.S.C. § 112, first paragraph, as failing the enablement requirement. Specifically, the Examiner contends that the specification is not

enabling for tablets comprising active ingredients other than pyridoxine hydrochloride and doxylamine succinate.

Applicant respectfully disagrees. The claims, prior to any amendment, were enabled and satisfied the requirements under § 112, first paragraph. However, in an effort to further prosecution and secure prompt allowance in this case, the claims have been amended to address the Examiner's concern. As indicated above, claim 9 is cancelled. Claim 6 now recites that the pharmaceutical tablet comprises "a therapeutically effective amount of doxylamine succinate as an active ingredient perceived as causing teratogenicity and a therapeutically effective amount of pyridoxine hydrochloride as another active ingredient...." Claim 35 also contains this language. The Examiner acknowledged that the specification is enabling for tablets comprising pyridoxine hydrochloride and doxylamine succinate as active ingredients. Action, page 2.

In view of the above, Applicant requests that the enablement rejection be withdrawn.

E. The Utility Rejection Is Overcome

Claims 6 and 9 are rejected under 35 U.S.C. § 101 as lacking patentable utility. The Examiner asserts that the claims are drawn towards encouraging women to take "a suspected teratogen." Action, page 3.

Applicant respectfully disagrees. Claims 6 and 9, prior to any amendments, were ***not*** directed to pharmaceutical tablets that encourage pregnant women to take a teratogenic substance by virtue of pregnancy-friendly indicia applied to tablets containing such a substance. To the contrary, nothing in the specification suggests that the active ingredients that may be comprised in a claimed pharmaceutical tablet are teratogenic. Instead, the present invention is directed to tablets containing active ingredients that are ***not*** teratogenic but that are presently, yet erroneously, ***perceived*** by pregnant women as causing teratogenicity, where this misperception

often causes them to stop a treatment that they should not. *See, e.g.*, specification, paras. [0015] and [0020]. Doxylamine succinate is one of such active ingredients, despite extensive published proof of the fetal safety of Diclectin™, which contains this ingredient. *Id.* at paras. [0012]-[0015].

However, in an effort to further prosecution and secure prompt allowance in this case, the claims have been amended for clarity. Again, as indicated above, claim 9 is cancelled. Claim 6 now recites that the pharmaceutical tablet comprises "a therapeutically effective amount of doxylamine succinate as an active ingredient perceived as causing teratogenicity and a therapeutically effective amount of pyridoxine hydrochloride as another active ingredient...." Claim 35 also contains this language.

The presently claimed invention is useful to pregnant women by having a practical impact on their perception of teratogenic risk, as statistically shown in the specification as filed, and thus on their compliance with a medically recommended regimen of doxylamine succinate and pyridoxine hydrochloride administration. *See, e.g.*, Example 2. In at least this regard, the claimed invention is a "new and useful... composition of matter." 35 U.S.C. § 101.

As the claimed invention satisfies the utility requirement, Applicant respectfully requests that the utility rejection be withdrawn.

F. The Obviousness Rejections Are Overcome

Claims 6 and 9 are rejected under 35 U.S.C. § 103(a) as being obvious over Orifer F Prenatal Vitamin Supplement (September 25, 1996) ("Orifer F") in view of WO 97/48384. Claims 6 and 9 are also rejected under 35 U.S.C. § 103(a) as being obvious over WO 97/48384 in view of Orifer F.

Applicant respectfully disagrees. The claims, prior to any amendment, were not rendered obvious by the cited references. However, in an effort to further prosecution and secure prompt allowance in this case, claim 6 has been amended to recite the following: "A pharmaceutical tablet destined for administration to pregnant women, said pharmaceutical tablet comprising a therapeutically effective amount of doxylamine succinate as an active ingredient perceived as causing teratogenicity and a therapeutically effective amount of pyridoxine hydrochloride as another active ingredient, said pharmaceutical tablet further comprising a graphical representation of a pregnant woman applied to the tablet surface, said graphical representation being visible to the naked eye." As noted above, claim 9 is cancelled.

Claim 6 is not obvious over the cited references for at least the reasons explained in the following subsections. The reasoning can also be applied to new claim 35.

1. Summary of the Argument

The obviousness rejection cannot be supported for several reasons, each of which, independently, render the rejection improper. For example, an assessment of the scope and content of the prior art and the differences between the prior art and the claimed invention does not lead to a conclusion of obviousness. As will be discussed in further detail below, the differences between the prior art and the claimed invention are not obvious differences. Moreover, there is no apparent reason to combine or modify the cited references in the manner suggested by the Examiner. Thus, a *prima facie* case of obviousness has not been established. However, even if a *prima facie* case of obviousness has been shown, which Applicant does not concede, secondary considerations effectively rebut such a showing. These secondary considerations include commercial success, long felt need and unexpected results associated with the claimed invention. Finally, any assertion that the claimed invention was "obvious to try"

necessarily fails. Not only has the Examiner failed to properly support such an assertion, but Applicant presents evidence and reasoning to the contrary. Each of these points will now be further examined.

2. An Assessment of the *Graham* Factual Inquiries Does Not Support An Obviousness Rejection

As noted in The Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.* ("the Guidelines"), the *Graham* factual inquiries are still the proper means by which obviousness should be determined. 72 Fed. Reg. 57256, 57527. These factual inquiries include determining the scope and content of the prior art, and ascertaining the differences between the claimed invention and the prior art. *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1 (1966)). As will be shown, an assessment of the factual inquiries as regarding Orifer F and WO 97/48384 and the claimed invention does not support an obviousness rejection because these references fail to render the claimed differences obvious. Moreover, there is no apparent reason to modify or combine the cited references as suggested by the Examiner.

a. The Present Invention

The presently claimed invention concerns a pharmaceutical tablet that comprises therapeutically effective amounts of two different active ingredients: doxylamine succinate and pyridoxine hydrochloride. As recited in the claims, doxylamine succinate is perceived as causing teratogenicity. This is also discussed in the specification. Specification, paras. [0012]-[0015]. The tablet is destined for administration to pregnant women. The tablet comprises a graphical representation of a pregnant woman applied to the tablet surface. The graphical representation is visible to the naked eye. A non-limiting example of a graphical representation

of a pregnant woman is shown in FIG. 1 of the originally-filed specification, which is described at paragraph [0027]. One of the objects of the present invention is to decrease the perception by pregnant women of teratogenic risk associated with active ingredients that are, in fact, not teratogenic, through the application of pregnancy-friendly indicia to a pharmaceutical tablet comprising such active ingredients. *Id.* at paras. [0022]-[0024].

b. The Scope and Content of the Prior Art

Regarding the scope and content of Orifer F, this reference discloses the figure of a pregnant woman on the packaging of a prenatal vitamin supplement. Each tablet contains a variety of vitamins, and the tablets are designed "for pregnant women".

WO 97/48384 discloses the general principle of marking the surface of solid rapidly disintegrating dosage forms using non-contact marking techniques such as laser imprinting and ink-jet printing. WO 97/48384, Abstract. The marking techniques are described in detail. *Id.* at page 3, line 13 through page 4, line 28. The dosage form may be a tablet. *Id.* at page 5, lines 1-4. While markings are discussed generally, no specific graphical markings appear to be mentioned. *Id.* at page 2, lines 27-29.

c. Differences Between Applicant's Claimed Invention and the Cited Art

There are several differences between the claimed invention and Orifer F. First, as acknowledged by the Office Action mailed June 13, 2006, page 4, Orifer F does not show pregnancy-friendly indicia on the dosage form itself; thus, Orifer F does not show "a pharmaceutical tablet... comprising… a graphical representation of a pregnant woman applied to the tablet surface," as presently claimed. Moreover, nothing in this reference discusses any practical effect from a graphical representation of a pregnant woman on a packaging, much less as applied to the surface of a pharmaceutical tablet. These facts were confirmed in the

Declaration of Dr. Gideon Koren, submitted with Applicant's Response to Office Action dated October 12, 2006, which is incorporated herein by reference. In addition, Orifer F comprises namely vitamins and does not appear to comprise any active ingredient that would *a priori* be perceived by pregnant women as possibly causing teratogenicity. More particularly, Orifer F does not comprise doxylamine succinate as an active ingredient perceived as causing teratogenicity, as presently claimed.

Many differences may be ascertained between WO 97/48384 and the presently claimed invention. For example, nothing in WO 97/48384 teaches or suggests "a pharmaceutical tablet... comprising... a graphical representation of a pregnant woman applied to the tablet surface," as presently claimed. The Examiner concedes as much by stating that no design having a graphical illustration of a pregnant woman is found in this reference. Action, page 5. Indeed, this reference fails to discuss pregnant women, or directing of any dosage form discussed therein towards pregnant women. In addition, nothing teaches or suggests any practical effect of any such representation imprinted on a pharmaceutical tablet on the perception of causing teratogenicity, or even generally in the context of pregnancy. While vitamins are mentioned in this reference, they are referred to as "secondary components" and not as an "active ingredient," as presently claimed. WO 97/48384, page 7, lines 32-25. Moreover, pyridoxine hydrochloride is not mentioned as a vitamin or active ingredient in WO 97/48384. This reference also fails to discuss doxylamine succinate in any context.

d. The Differences Between Applicant's Claimed Invention and the Cited Art Are Not Obvious Differences

The United States Supreme Court in *KSR* explained the importance "to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior

art] elements" in the manner claimed. *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1741 (2007). The Court noted that there should be an "explicit" analysis regarding "whether there was an **apparent reason** to combine the known elements **in the fashion claimed** by the patent at issue." *Id.* (emphasis added).

i. Differences between the claimed invention and the cited art are not obvious

The numerous differences between the claimed invention and the cited art are not obvious differences. At a minimum, neither reference discusses applying a graphical representation of a pregnant woman to the surface of a pharmaceutical tablet, as presently claimed. As discussed above, Orifer F only shows such an image on its packaging, and WO 97/48384 does not describe or show such an image whatsoever. Indeed, neither reference addresses any reason for or benefit from applying a graphical representation of a pregnant woman to the surface of a pharmaceutical tablet, much less a tablet comprising pyridoxine hydrochloride and doxylamine succinate.

These factual differences between the claimed invention and the cited art cannot lead to a conclusion that Orifer F and WO 97/48384, taken together or separately, render the present claims obvious. For at least this reason, Applicant respectfully requests that the obviousness rejection be withdrawn.

ii. There is no apparent reason to modify Orifer F or WO 97/48384 in the manner suggested by the Examiner

In view of the differences between the cited references and the present invention, Applicant finds no apparent reason to modify Orifer F using the teachings of WO 97/48384, or *vice versa*, in the manner suggested by the Examiner. For example, Orifer F neither teaches nor suggests a pharmaceutical tablet that comprises an active ingredient perceived as causing

teratogenicity, much less doxylamine succinate as such an active ingredient. Indeed, nothing in this reference speaks to the concept of a perception of teratogenicity of any ingredient therein. WO 97/48384 fails to address these deficiencies. Thus, there is no apparent reason to modify Orifer F with methods taught by WO 97/48384 to arrive at the claimed pharmaceutical tablet comprising a therapeutically effective amount of doxylamine succinate as an active ingredient perceived as causing teratogenicity.

Moreover, nothing in WO 97/48384 teaches or suggests imprinting any pregnancy-friendly indicia on any pharmaceutical tablet. Indeed, the examples taught by WO 97/48384 of a mark or text that may be applied to a dosage form surface include "a company logo or name, a product name, a trade mark, or a number indicating the amount of active ingredient in the dosage form." WO 97/48384, page 2, lines 27-29. These types of marks are merely for identification purposes, such as identifying the source of the dosage form or identifying the amount of an ingredient in the dosage form. Nothing in this reference suggests applying any sort of pregnancy-friendly mark to a tablet that addresses the perception of teratogenicity of an active ingredient comprised therein. Thus, there does not appear to be any apparent reason why a skilled artisan would modify WO 97/48384 with the teachings of Orifer F.

e. Conclusion

Not only are the differences between the cited references and presently claimed invention not obvious differences, but there is no apparent reason to modify either reference with the teachings of the other in the manner suggested by the Examiner. For at least these reasons, a *prima facie* case of obviousness has not been established. Applicant therefore respectfully requests that the obviousness rejection be withdrawn.

3. Secondary Considerations Support a Finding of Non-Obviousness

Even if the Examiner has properly set forth a *prima facie* case of obviousness, which Applicant does not concede, Applicant may still overcome the obviousness rejection through a showing of secondary considerations such as unexpected results, long felt need, or commercial success. *KSR*, 127 S.Ct. at 1734 (confirming that secondary considerations are relevant to the obviousness analysis). As noted in the Guidelines, secondary considerations "must be evaluated by Office personnel" when considering whether a claimed invention is obvious. 72 Fed. Reg. at 57527. When the claimed invention is evaluated in view of these secondary considerations, the obviousness rejection cannot stand.

a. Commercial Success

In the Response to Office Action dated October 12, 2006 ("the October 2006 Response"), Applicant set forth evidence of commercial success regarding Diclectin™, a product that contains a combination of pyridoxine hydrochloride and doxylamine succinate. This evidence and the related arguments from the October 2006 Response are incorporated herein by reference. As noted in that Response, sales of Diclectin™ significantly and unexpectedly increased in the year that followed the application of a graphical representation of a pregnant woman on the commercialized Diclectin™ tablets, and those sales could be directly attributed to the applied graphical representation since nothing else was modified in the medicament itself, or in the sales and marketing of the drug. This was explained by Eric Gervais in his Declaration submitted with the October 2006 Response, which is also incorporated herein. The Examiner makes no reference to this evidence or the Declaration. As such, it appears the Examiner improperly failed to consider this evidence of commercial success. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (stating that "***all*** evidence of nonobviousness must be considered when assessing

patentability") (emphasis added). Applicant maintains that Applicant's previous Response was sufficient to overcome the obviousness rejection.

b. Unexpected Results

In the October 2006 Response, Applicant set forth evidence of unexpected results associated with the claimed invention. This evidence and the related arguments from the October 2006 Response are incorporated herein. As previously noted in the October 2006 Response, Example 2, in particular, demonstrates the clinically significant and statistically reliable effect of placing a graphical representation of a pregnant woman on the surface of a pharmaceutical tablet, as compared to plain tablets without any indicia. The Examiner makes no reference to this data. Indeed, it appears the Examiner overlooked this data as the Examiner seems to contend that the present invention fails to address the problem of overcoming pregnant women's misperception of presumed teratogenicity of ingredients in a tablet. Action, page 5. As discussed in the previous Response and below, Example 2 in the present specification demonstrates that this problem is overcome by the claimed invention. As such, it appears the Examiner improperly failed to consider this evidence of unexpected results. *See In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (stating that "***all*** evidence of nonobviousness must be considered when assessing patentability") (emphasis added). Moreover, Applicant maintains that Applicant's previous Response was sufficient to overcome the obviousness rejection. Despite this sufficiency, Applicant provides further comments and evidence regarding unexpected results associated with the claimed invention.

i. Additional evidence pertaining to Example 2

As noted above, the results set forth in Example 2 of the present specification provide proof that the application of a graphical representation of a pregnant woman to the surface of the

claimed pharmaceutical tablet resulted in a marked decrease in the perception of teratogenic risk associated with ingredients in the tablet. Indeed, in the Declaration of Dr. Koren, submitted with the October 2006 Response and also incorporated herein, Dr. Koren stated, "***The results reported in the '803 application are unexpected.*** One having practical knowledge of paediatrics and obstetrics would have expected little or no clinical effect stemming from graphical representations placed on dosage forms." Koren Declaration, para. 11.2 (emphasis added). Further, an article published in early 2007 by Dr. Koren confirms the clinical relevance of the Visual Analog Scale (VAS) as an objective measuring tool of women's perception of teratogenic risk, as well as the statistical significance of the results shown in Example 2. *Can. J. Clin. Pharmacol.* 14(1) Winter 2007:e10-e16; January 5, 2007 (Appendix 1). In this article, Dr. Koren indicates that the present invention is an "important means to increase compliance" in the context of decreasing misperceptions of teratogens in medications directed to pregnant women, thus clearly recognizing the clinical significance of the claimed graphical representation of a pregnant woman on pharmaceutical tablets. *Id.* at page e15.

ii. Recognition by Health Canada

Applicant further notes that the presently claimed invention has been well recognized and approved by a governmental agency and by renowned peers, and that the previous plain white Diclectin™ tablet has been completely replaced in industry by Diclectin™ bearing a graphical representation of a pregnant woman, as recited in the present claims. For example, the Ministry of Health Canada approved an amendment to the Diclectin™ product monograph in June 2005, which added this information: "Tablets are imprinted with the pink image of a pregnant woman." Page 10 of monograph (Appendix 2). The monograph also discusses the significance of the graphical representation, first stating that, "Noncompliance in the use of prescription

medications is common among pregnant women owing to fear over fetal exposure and safety even in the case of drugs with appropriate safety data." *Id.* A discussion of the experimental results as set forth in Example 2 of the present specification is then presented, followed by this conclusion: "By reducing the perception of teratogenic risk by pregnant women the pregnancy indicia may increase compliance and thus the effectiveness of Diclectin®". Thus ***Health Canada recognized and approved of the clinical significance of the claimed graphical representation***. Indeed, the results were significant enough to warrant their inclusion in the monograph. Moreover, these statements also suggest a long felt need in the medical field for a mechanism to lower pregnant women's perceptions of teratogenic risk associated with pharmaceutical ingredients that are not harmful to a fetus—a need the claimed invention addresses.

c. Conclusion

All of the objective evidence provided in the foregoing is commensurate with the scope of the present claims. As such, these secondary considerations overcome any *prima facie* showing of obviousness. Applicant therefore respectfully requests that the obviousness rejection be withdrawn.

4. Obvious to Try

The Examiner appears to apply an "obvious to try" standard to the presently claimed invention. Applicant disagrees with the conclusion of obviousness reached by the Examiner in this regard.

a. The Examiner Has Not Properly Established That the Claimed Invention Was "Obvious To Try"

In *KSR*, the Court provided the following comments regarding basing an obviousness rejection on the concept of "obvious to try":

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under 35. U.S.C.S. § 103.

127 S.Ct. at 1742. At a minimum, the Examiner has failed to show the following: (1) the existence of a finite number of identified, predictable solutions regarding overcoming pregnant women's perception of teratogenic risks of non-teratogenic ingredients in pharmaceutical tablets; (2) that applying a graphical representation of a pregnant woman onto the surface of a pharmaceutical tablet was a known option within the technical grasp of a skilled artisan; and (3) that the results achieved by applying such a representation to a tablet resulted in anticipated success. In view of these deficiencies, it cannot be said that the Examiner has carried his burden in showing that the claimed invention was "obvious to try".

In the present case, Applicant respectfully submits that there could well have been no practical effect whatsoever of applying a graphical representation of a pregnant woman on a Diclectin™ tablet. Dr. Koren confirmed this possibility was likely in his Declaration submitted with the October 2006 Response: "One having practical knowledge of paediatrics and obstetrics would have expected little or no clinical effect stemming from graphical representations placed on dosage forms." Koren Declaration, para. 11.2.

b. There Is No "clear cut expectation of success"

In the present Action, the Examiner states the following:

> While applicant argues obvious to try was not a standard, it is clear that any design could at the [time the WO 97/48384 application was filed], be imprinted on a tablet-with a clear cut expectation of success; no trial is needed. It remains only to apply a design representative of the effects or use expected...."

Action, page 5. Applicant notes that, in the context of asserting that the present invention was "obvious to try", the Examiner appears to assert that applying a design "representative of the effects or use expected" on a tablet, such as the graphical image of a pregnant woman found in Orifer F, results in a "clear cut expectation of success" with respect to the present invention. Action, page 5. However, the Examiner provides no authority or factual evidence for this statement. To the extent that the obviousness rejection is based on this reasoning, then, the rejection is improper. *See* MPEP § 2142 ("The examiner bears the initial burden of ***factually supporting*** any *prima facie* conclusion of obviousness.") (emphasis added). If this position is based on the Examiner's personal knowledge, then Applicant requests the Examiner provide an affidavit as required under 37 C.F.R. § 1.104(d)(2). Moreover, Applicant further notes that "[i]nventors generally are optimistic about what they choose to experiment with, but that does not necessarily suggest obviousness." *Pfizer Inc. v. Apotex Inc.*, 488 F.3d 1377 (Fed. Cir. 2007) (J. Lourie, dissenting).

5. Conclusion

The legal arguments and objective evidence set forth above overcome the obviousness rejection with respect to claim 6. Similarly, new claim 35 is also not obvious. Applicant therefore respectfully requests that the rejection be withdrawn.

G. The Claimed Graphical Representation Of A Pregnant Woman Would Not Be Interpreted As A "Fat Lady"

The Examiner appears to assert that as an alternative to being interpreted as a picture of a pregnant woman, the claimed graphical representation could have been interpreted by test subjects as merely a "fat lady": "Alternatively, the depiction is seen as a fat lady; thus the good market data." Action, page 5. In this statement, the Examiner also appears to suggest that the "good market data" (which is presumably the data presented in Applicant's previous Response) could be associated with the perception of the graphical representation as being a "fat lady". However, both suggestions do not align with either the general teachings of the specification, nor the results of Example 2. When reading the claims in view of the specification, as is proper, the claimed invention does not support either assertion. *See, e.g.*, MPEP § 2173.02.

For example, there is no evidence in the specification or otherwise to suggest that a pregnant woman handed a pharmaceutical tablet intended for pregnant women, wherein the tablet has a graphical representation of a pregnant woman applied to its surface, would view the representation as a "fat lady". One reading the present specification would not conclude this, either, as pregnancy-friendly indicia and graphical representations of a pregnant woman are discussed throughout the specification. Moreover, there is no evidence to suggest that the "good market data" could be associated with pregnant women's perception of the graphical representation as being a "fat lady". Indeed, there appears to be no evidence or reasoning to support these apparent assertions by the Examiner. To the extent that these assertions are used to support any rejection issued by the Examiner, those rejections are improper.

H. The Obviousness-Type Double Patenting Rejection Is Overcome

Claims 6 and 9 are rejected for non-statutory obviousness-type double patenting as being unpatentable over claim 1 of Gervais *et al.* (U.S. Patent No. D501252) in view of Kirschner *et al.* (U.S. Patent No. 6,352,713B1).

Applicant disagrees with the obviousness-type double patenting rejection. For example, Gervais *et al.* specifies no active ingredient, and the combination of Gervais *et al.* in view of Kirschner *et al.* fails to teach "[a] pharmaceutical tablet destined for administration to pregnant women, said pharmaceutical tablet comprising a therapeutically effective amount of doxylamine succinate as an active ingredient perceived as causing teratogenicity and a therapeutically effective amount of pyridoxine hydrochloride as another active ingredient, said pharmaceutical tablet further comprising a graphical representation of a pregnant woman applied to the tablet surface, said graphical representation being visible to the naked eye."

However, in an effort to further prosecution and secure prompt allowance in this case, Applicant files herewith a terminal disclaimer over U.S. Patent No. D501252 to Gervais *et al.* As such, the obviousness-type double patenting rejection is moot, and Applicant respectfully requests that it be withdrawn.

I. Conclusion

Applicant believes that this is a complete response to the Final Office Action mailed October 5, 2007. The present claims are in a condition for allowance, and such favorable action is requested.

The Examiner is invited to contact the undersigned Attorney at (512) 536-3015 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

Tamara A. Kale
Reg. No. 53,087
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3020
(512) 536-4598 (facsimile)

Date: March 5, 2008

APPENDIX 1

THE WAY WOMEN PERCEIVE TERATOGENIC RISK

Gideon Koren

The Hospital for Sick Children, Toronto, Ontario, Canada

Corresponding Author: gkoren@sickkids.ca

Because of increased anxieties of drug-induced congenital malformations, women and physician alike fear drug therapy in pregnancy even in life-threatening situations. The goal of counseling women on their teratogenic risk is to present to them an accurate, up-to-date estimate of their benefit to risk ratio. However, the same data may be received and interpreted very differently by different patients, leading them to individual conclusions and finally to the decision to continue or terminate pregnancy.

In both North America and Europe there are high rates of elective abortions[1,2] and while pregnancies are terminated for a variety of reasons, incorrect perception of a teratogenic risk may be an important factor. Most women who have been made aware of major malformations or chromosomal aberrations through ultrasound or amniocentesis choose to terminate pregnancy.[3] As documented by the Greek experience after the Chernobyl disaster, even an unbiased suggestion of adverse fetal outcome may prompt women to terminate pregnancy "to be on the safe side".[4]

This phenomenon has been painfully demonstrated in the case of radio diagnostic procedures performed during pregnancy. Many associate "radiation" with the effects of the atomic bomb and other nuclear disasters that have come about in world history. Usually, radio diagnostic procedures involve fetal exposures to low doses of ionizing radiation in the realm of less than 5 rad. This level of exposure is not considered to be teratogenic.[5] In spite of this many pregnant women exposed to such radiation are rather concerned and consider termination of their pregnancy. Even after information is provided in regards to the safety of specific radio diagnostic procedures, their perception of teratogenic risk remains well above the baseline population risk.[6]

Special attention and consideration should be given when counseling pregnant women exposed to low-dose ionizing radiation. At Motherisk, we have been continuously impressed by the number of cases of misperception and distorted information regarding the potential teratogenic risk of drugs and chemicals. In particular, we felt that many women tend to assign an unrealistically high risk to medications not known to be teratogenic. In some cases, this misperception has led to termination of pregnancy.

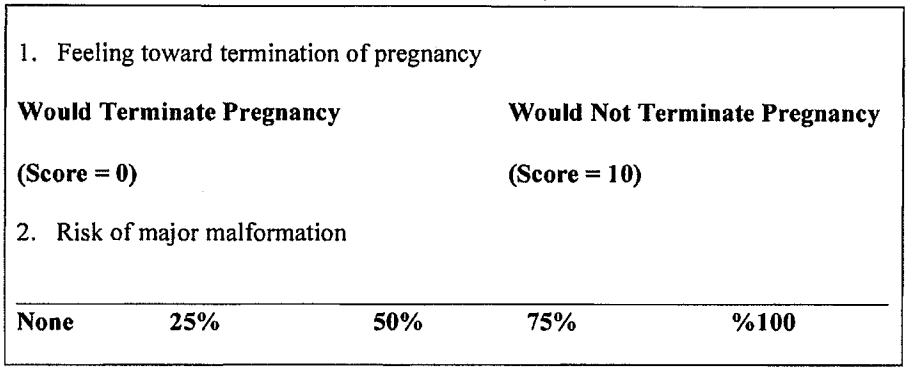
In an attempt to objectively quantify women's perception of their teratogenic risk, we created a 10 cm visual analog scale. After collection of patient's data, and before delivering our view of the apparent risk, women are asked to assign to their perceived risk for major malformations a number between 0% and 100%. We also ask what, in their opinion, is the risk for major malformations in the general population, because their knowledge of baseline risk is crucial for their perception of their own risk. In addition, patients are asked to quantify from 0% to 100% their tendency to terminate or continue pregnancy.

The completion of this questionnaire is followed by informing the patient of all known information about the exposure(s) in question. Subsequently, the questionnaire is repeated. Patients are urged to express their own views and not to answer the questionnaire in a way they might think would please the interviewer. Analysis of the first 80 cases on which the visual analog scale (VAS) was used between September and December 1986 reveals the power of this tool in detecting misperception and misinformation.[7]

Before receiving up-to-date information about the specific exposure, women exposed to nonteratogens assigned a mean risk of 24 ± 2.8% for major malformations. After the interview, however, the risk was perceived as lower (14.5 ± 3%, $p<0.01$). The risk for major malformations in the general population was estimated as 5.6 ± 1.3%, which is comparable to the real figure in the

literature. The perceived risk before and after our intervention was significantly different from that estimated by the patients for the general population. The tendency for continuation of pregnancy showed a significant change following the interview (from 7.9 ± 0.3 to 8.7 ± 0.3 in the analog scale, $p<0.01$).

FIG. 1 Visual Analog Scale



Eleven patients were exposed to medications known to be teratogenic. Their perceived teratogenic risk was unchanged (36.2 ± 11.7% before and 36.7 ± 15.6% after the interview). Their tendency for termination/continuation of pregnancy did not change following the interview. Three of them did decide to terminate pregnancy within a few weeks of the consultation.

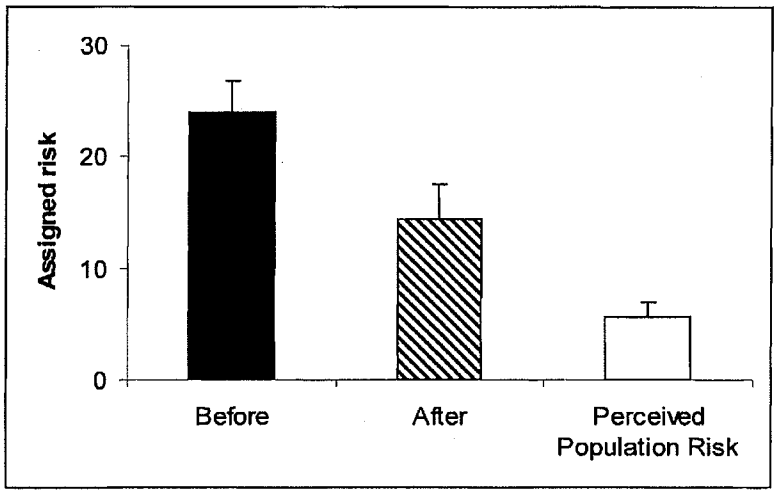
Eleven of our patients were single mothers. Although they did not perceive their risk differently from married women, those who had been exposed to nonteratogens showed a significantly higher tendency to terminate pregnancy before the interview (4.7 ± 1.2 on VAS units single mothers vs. 8.1 ± 0.4 married, $p<0.05$). Following the intervention, their perception significantly changed, being less likely to terminate their pregnancy (7.4 ± 1.2, $p<0.05$) but the VAS was still different from married women.

No correlation was found between estimation of risk (or tendency to terminate/continue pregnancy) and number of preparations consumed by the woman, age, parity, or socioeconomic status. No differences in perception of risk were detected between women referred by physicians and those who were self-referred. This analysis highlights that pregnant women exposed to nonteratogenic agents believe they have a risk of 1 in 4 of having a child with major malformations. This figure is very close to the known risk of thalidomide.[8] Importantly, these women estimated the risk in the general population to be 5%, which is similar to the real figure of 4-5%.[9] This means that the concept of teratogenic risk was well understood and that women were all informed about the risk in the general population. In addition, it lends clinical significance to the unrealistically high risk assigned by these women to their nonteratogenic exposures.

This phenomenon was well described in our study where women with nausea and vomiting of pregnancy (NVP) in their first trimester were prospectively followed. Over three-quarters of the 260 women enrolled initially believed that pharmacologic treatment of NVP increased their teratogenic risk. After having been counseled in regard to the extensive literature on the safety of anti-emetics (other than thalidomide which is the only medication ever to have been positively proven to cause birth defects), these women were followed up at 20 weeks' gestation. The risk perceived decrease significantly after counseling.[10]

Two basic reasons can be put forward to explain the unrealistically high teratogenic risk assigned by pregnant women: misinformation and misperception.

FIG. 2 Patient-assigned risk of major malformation for parents not exposed to teratogens



Misinformation

Advisories on potential teratogenic risk appear constantly in the lay media, usually to stress risks, and very rarely to address the safety of specific drugs. Analysis of 15 different popular magazines disclosed poor scientific standards and a clear tendency to be misleading or inaccurate.[11] There was a tendency to alarm readers without justification. In addition, popular books dealing with pregnancy often tend to assign risk to drugs not proven to be risky.

For example the author of, *Will My Baby Be Normal?* states, "Do not take any aspirin or medication that include aspirin if you think you might be pregnant. Midline body defects have been attributed to this drug".[12] Such defects are not believed to be associated with salicylates in humans. In yet another instance, J. Elkington entitled his book on reproductive toxicology, *The Poisoned Womb*, although most of the data discussed do not prove poisoning in humans.[13] Possible sources of misinformation are the *Physicians' Desk Reference* and the *Martindale*, which includes warnings on exposures during pregnancy that are no longer correct. Reference books dealing with drug use in pregnancy have been published[9,14,15] and should be used by physicians caring for women in pregnancy.

Another source of misinformation is physicians. We have dealt with more than a few cases in which physicians advised women to terminate pregnancy despite non teratogenicity (Figure 3). This may reflect a defensive approach in the current litigious atmosphere, or the possibility that physicians themselves are misinformed. Our data indicate that women referred by physicians did not have a more accurate perception of risk than self-referred patients.

A prime example of physician misinformation is seen with the use of cocaine. To date, there has been really no evidence to suggest that cocaine increases teratogenic risk in any meaningful way above the population baseline. However, a survey administered by us[16] revealed that the majority of participating physicians felt that malformations were associated with cocaine use. These same physicians would also wish to terminate a pregnancy where exposure to cocaine occurred during the first 8 weeks of gestation. This is alarming, as physicians' erroneous perceptions may lead them to offer women unjustified terminations of pregnancy. Fortunately the same analysis showed that, in most cases, counseling pregnant women exposed to cocaine are successful in changing their tendencies towards termination.

FIG. 3 Letter of a Motherisk patient who had been advised by other physicians to terminate pregnancy

> *"Last December, I sought your help regarding a couple of tranquilizers I had taken within the first few weeks of my pregnancy. The prescribing doctor and a well-respected obstetrician had suggested that I abort the pregnancy.*
>
> *As a result of your advice, my husband and I are the ecstatic parents of a beautiful, healthy baby girl. I cannot thank you enough. The work you are doing is a wonderful necessity. If there is anything I can do for your program on a volunteer basis, I would be more than happy to be of assistance".*

Misperception

Our experience shows that even after we had advised women that medications taken by them did not increase their risk of having a malformed child, their own *perceived* risk was significantly higher than their *perception* of risk in the general population.

It is conceivable that during pregnancy there is an increased sensitivity to this issue, leading to a distorted perception of risk. Of special interest is the approach of single mothers: while assigning a teratogenic risk similar to married women before receiving our advice, they were much less ready to continue pregnancy with such a risk. Single mothers may have a variety of psychological, moral, and socioeconomic reasons to discontinue pregnancy. For them, a distorted perception of teratogenic risk may be the last straw in the decision to terminate pregnancy.

Our intervention appears to have significantly changed the perception of women exposed to nonteratogenic agents in terms of estimating the risk as well as in the tendency to terminate/continue. This tendency was best documented in the subgroup of single mothers, in which some of the women who were already booked for dilatation and curettage decided to carry on the pregnancy.

If post-interview assessment still revealed an unrealistically high perception of risk or tendency to terminate pregnancy, we would spend additional time to explain to the woman that her apparent risk, based on current knowledge, is lower than the one perceived by her. We have recently shown that appropriate counseling can empower the majority of women who discontinued their psychotropic drugs to resume their use.[7]

It may be argued that women contacting a consultative service such as Motherisk are a selected group of patients with a higher degree of concern, and therefore their perception does not accurately represent the total population of pregnant women. Yet, it is such individuals who are more likely to decide to terminate pregnancy, based on wrong information.

It is also possible that some women who are ambivalent about continuing their pregnancy seek a legitimate medical reason for termination. In both cases, accurate information will help the woman and her family to make a knowledgeable decision.

The Impact of Risk Perception on Women's Decision to Continue Pregnancy

In an attempt to assess the relevance of the risk perception as measured by us in predicting women's apparent decision about their pregnancy, we analyzed the 123 women who expressed a tendency of 50% or more to terminate their pregnancy between September 5, 1986 (the date the VAS was first introduced) and January 29, 1988 (Table 1).

TABLE 1 Study Population

Women who tended ≥ 50% to terminate their pregnancy prior to information	**123**
Women who tended ≥ 50% to continue their pregnancy	**246**
EXCLUSIONS	
Prospective cases (not yet pregnant)	**5**
Refusals to follow-up	**3**
Lost for follow-up	**7**
Had not reached EDC	**30**
STUDY COHORT (N=78)	
Decided to continue pregnancy (CP)	**61**[a]
Decided to terminate (TA)	**17**

[a]Outcome as follows: 57 normal infants, 4 miscarriages

At the time of the consultation all 123 women verbally expressed serious consideration of terminating their pregnancy and documented this on the VAS. Of these, the following were excluded from further analysis: 5 came for prospective advice and did not become pregnant until the analysis of the data; 3 refused to participate in the telephone follow-up; 7 could not be reached at the contact telephone numbers; and 30 had not yet reached their expected date of confinement (EDC). Thus, our study group consisted of 61 women who decided to continue their pregnancy despite their initial tendency and 17 who chose to terminate their pregnancy.

The two groups [continued pregnancy (CP), n=61, and therapeutic abortion (TA), n=17] did not differ statistically in their mean age, number of pregnancies, number of previous live births, therapeutic or spontaneous abortions, or number of exposures in the pregnancy of question, where "exposures" included every medical preparation, chemical, or radiation reported during the consultation.

The tendency to terminate pregnancy before receiving the relevant medical information did not differ significantly between the CP and TA groups (34.3 ± 2.5% vs. 24.8 ± 5.4%, respectively, $p>0.05$). Following the interview, however, there was a highly significant difference in the response of the two groups: women who eventually terminated their pregnancies had a non significant increase in the tendency to continue pregnancy and in most cases did not pass the 50% point (24.8 ± 5.4% to 45.1 ± 9.8%) ($p>0.1$). Their tendency to terminate pregnancy after the counseling process was significantly different from the CP group ($p<0.0001$).

Of 61 women in the CP group, 4 had a miscarriage between 8 and 12 weeks of gestation. The other 57 women had normal pregnancy outcomes, with no apparent major malformations or developmental delay up to 9 months of postnatal age. Table 2 presents the analysis of the 17 women who chose to terminate their pregnancy. In two cases, women were exposed to drugs known to have adverse fetal outcome (BCNU for mycosis fungoides and warfarin for prosthetic valve), and in a third case an amniocentesis done because of maternal age (>35 years) tested positive for Down's syndrome.

Of interest, one woman exposed to non teratogens claimed in the follow-up interview that her decision to terminate pregnancy was based on the information she received during the Motherisk consultation; however, the summary letter sent to her physician clearly stated that she did not have an increased teratogenic risk. One woman attributed her decision to advanced age and poor gynecological history, and another had an increased genetic risk for major malformations. In two cases, the women claimed that their obstetricians encouraged them to terminate pregnancy owing to a high teratogenic risk (up to 80%) despite our advice of no such increased risk. Eight women who perceived their teratogenic risk as high despite our advice indicated that this was their main reason for termination; four of them were unmarried.

Of the 78 evaluable pregnancy patients who intended to terminate their pregnancy prior to our consultation, it is probable that we reversed the tendency in 61 (57 normal healthy babies and 4 miscarriages). Although it is impossible to prove that all these pregnancies would have been terminated without our intervention, it is conceivable that this might have been the case, since most women who showed a greater than 50% tendency to terminate pregnancy after our intervention eventually did so. The two groups,

TA and CP, did not differ in a large number of characteristics and had very similar rates of drug exposures. However, most of the 17 cases in the TA group expressed obvious explanations, unrelated to the exposures in question, as factors that led them to decide to terminate their pregnancy. Four of them were unmarried; in the analysis above we have shown that single mothers, despite estimating their teratogenic risk in a similar manner to married women, have a significantly higher tendency to terminate their pregnancy.

TABLE 2 Analysis of reasons for therapeutic abortion as indicated by the women

REASON	Number of Cases [a]
Exposure to drug with potential adverse fetal effect	2
Down's syndrome detected in amniocentesis	1
Advanced age with poor gynecological history	1
Higher genetic risk for major malformations	1
Advised to terminate pregnancy by obstetricians despite exposure to nonteratogens	2
Unmarried women	4
Fears of higher teratogenic risk despite Motherisk advice	8
Claimed termination was according to Motherisk advice (not confirmed by summary letter)	1

[a]Total exceeds 17 (the number of women who chose to terminate their pregnancy) because some women had more than one reason for termination

After confirming the clinical relevance of the VAS, we now use the information collected not only for epidemiological endpoints, but also for individual cases. For example, if after the interview the woman has a tendency of termination higher than 50%, it is probably that she will not continue her pregnancy. If we are impressed that the teratogenic risk is the main reason for her tendency, and not other social, psychological, or personal reasons, we extend the interview to explain again the lack of risk associated with her exposure. The same insight is employed to counsel women exposed to teratogenic agents, if their perception does not reflect realization of an increased risk.

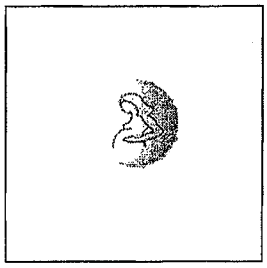
Empowering Pregnant Women to Take Medications

There are situations where women avoiding taking medications can have a major effect on their health, and even life-threatening. Such is the case with severe depression, where we have recently shown that appropriate counseling can empower the majority of depressed women who discontinued their psychotropic medications "cold turkey" to resume therapy. Prior to restarting their medications, many of the women had severe worsening of their symptoms.[17]

In a novel initiative, a Canadian manufacturer has introduced a silhouette of a pregnant woman as indicia to morning sickness tablets (Figure 4). In an observational, cross sectional study, perception of teratogenic risk among volunteer women was compared between a plain white tablet versus a white tablet with an image of a pregnant woman. The difference in teratogenic risk perception was highly significant ($p<0.0001$). In the survey group of 132 pregnant women, the mean perception of teratogenic risk was decreased by 23.4% when viewing tablets imprinted with the image of a pregnant woman. (Unpublished data)

While these findings must await more studies in pregnant women, this may be an important means to increase compliance and hence effectiveness of medications in pregnancy, with a parallel decrease in morbidity and need for hospitalization.

FIG. 4 Example of indicia used on a tablet to encourage women to use the product in pregnancy



APPENDIX 2

DUCHESNAY

PRODUCT MONOGRAPH

Pr DICLECTIN®

Doxylamine succinate, pyridoxine hydrochloride delayed release tablets

(10 mg/10 mg)

Antinauseant against Nausea and Vomiting of Pregnancy

(DIN 00609129)

Duchesnay Inc.
2925 boul Industriel
Laval, Quebec
Canada, H7L 3W9

Date of Revision:
June 17, 2005

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION **3**
SUMMARY PRODUCT INFORMATION 3
INDICATIONS AND CLINICAL USE 3
CONTRAINDICATIONS 3
WARNINGS AND PRECAUTIONS 3
ADVERSE REACTIONS 5
DRUG INTERACTIONS 6
DOSAGE AND ADMINISTRATION 6
OVERDOSAGE 7
ACTION AND CLINICAL PHARMACOLOGY 8
STORAGE AND STABILITY 10
SPECIAL HANDLING INSTRUCTIONS 10
DOSAGE FORMS, COMPOSITION AND PACKAGING 10
DISEASE MANAGEMENT AND SURVEILLANCE PROGRAM 10

PART II: SCIENTIFIC INFORMATION **12**
PHARMACEUTICAL INFORMATION 12
CLINICAL TRIALS 13
DETAILED PHARMACOLOGY 17
TOXICOLOGY 18
REFERENCES 20

PART III: CONSUMER INFORMATION **22**

Diclectin®

(Doxylamine succinate, pyridoxine hydrochloride)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 - Diclectin® Summary Product Information

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	tablet, 10 mg/10 mg	None

INDICATIONS AND CLINICAL USE

Diclectin® (doxylamine succinate and pyridoxine hydrochloride) is indicated in cases of nausea and vomiting of pregnancy.

CONTRAINDICATIONS

Patients who are hypersensitive to doxylamine succinate or pyridoxine hydrochloride.

WARNINGS AND PRECAUTIONS

General

Due to the anticholinergic properties of antihistamines, caution should be used when Diclectin® is taken concurrently with other medications or alcohol.

Carcinogenesis and Mutagenesis

A case-control investigation was performed by the Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) to analyze the incidence of childhood cancer in relation to the maternal consumption of doxylamine succinate, dicyclomine hydrochloride and pyridoxine hydrochloride. Dicyclomine hydrochloride was a component of the earlier formulations intended for nausea and vomiting of pregnancy that has since been removed due to a lack of evidence of contribution to efficacy.

Data were derived from interview reports and medical records of 555 mothers of children (under 15 years of age) with cancer and 1110 mothers of matched control children. Maternal ingestion of the antiemetic drug during the index pregnancy was not associated with increasing the risk of childhood malignant disease. No dose-response relationship was evident (1).

Dependence/Tolerance

There is no information to indicate that abuse or dependency occurs with the concentration of doxylamine succinate and pyridoxine hydrochloride found in Diclectin®.

Special Populations

Pregnant Women - Category A: Diclectin® is intended for use in pregnant women. There has been a vast clinical experience (> 30 million pregnancies worldwide) regarding the use of a combination of doxylamine succinate, pyridoxine hydrochloride with or without dicyclomine hydrochloride in this population (2).

Diclectin® has been the subject of many epidemiological studies (cohort, case control and meta-analyses) designed to detect possible teratogenicity. Two separate meta-analyses have been conducted that have assessed pregnancy outcome following the use of a combination of doxylamine succinate, pyridoxine hydrochloride with or without dicyclomine hydrochloride during the first trimester. McKeigue et al. (3) conducted a meta-analysis of 16 cohort and 11 case-control studies published between 1963 and 1991. No increased risk for malformations was found in first trimester exposures to doxylamine succinate and pyridoxine hydrochloride, with or without dicyclomine hydrochloride. A second meta-analysis, conducted by Einarson et al. (4) incorporated 12 cohort and 5 case-control studies. No statistically significant relationships were found between first trimester use of the combination doxylamine succinate, pyridoxine hydrochloride with or without dicyclomine hydrochloride and fetal abnormalities.

In 1989, a report on the safety of Diclectin® for use in the management of nausea and vomiting of pregnancy was prepared by a panel of experts for the Special Advisory Committee (5) on Reproductive Physiology to the Health Protection Branch of Health Canada. The Motherisk Program at the Hospital for Sick Children systematically reviewed the literature to develop an evidence-based algorithm on the safety and efficacy of treatments for nausea and vomiting of pregnancy. Doxylamine succinate combined with pyridoxine hydrochloride (Diclectin®) is listed as first line therapy on this algorithm (6). Similarly, the 2002 Society of Obstetricians and Gynaecologists of Canada (SOGC) Clinical Practice Guidelines on the management of nausea and vomiting of pregnancy recommend that this formulation be the standard of care, since it has the greatest evidence to support its safety and efficacy (7).

Atanackovic et al. (8) evaluated the safety of higher than standard doses of Diclectin® in 225 pregnant women with Nausea and Vomiting of Pregnancy (NVP) in an observational, prospective study. A total of 123 women received standard doses of up to 4 tablets a day and 102 women received a higher than standard dose ("supradose") of 5 to 12 tablets/day. Despite a twice larger mean maximal dose of Diclectin®, women receiving the supradose did not report more prevalent adverse effects while taking Diclectin®. The lack of any major malformation with the supradose strongly suggests that the higher dose is not teratogenic. It was concluded that supradoses of 5 to 12 tablets daily did not appear to affect the incidence of maternal adverse effects or pregnancy outcome.

Baseline Risk: The background baseline risk of major malformations for all pregnancies is approximately 1-3%. This is the risk of having a child with a birth defect when no teratogenic exposure occurs in pregnancy. This underlying risk may be increased due to maternal age, medical or family history, or exposures to certain drugs, chemicals or levels of radiation known to cause birth defects. Published data clearly shows that Diclectin® use in pregnancy does not increase a woman's baseline risk of having a child with a major malformation (9-12). Diclectin® has the highest safety rating in Briggs: "Category A."(13). No other prescription drug has been more extensively studied for safety in pregnancy (5).

Nursing Women:

There are no published reports describing the use of Diclectin® during lactation. However, the passage of doxylamine succinate into breast milk can be expected. Effects on a nursing infant, if any, are unknown, but

sedative and other antihistamine actions are a potential concern. Pyridoxine hydrochloride is excreted into breast milk, but in the doses provided in Diclectin®, presents no risk to a nursing infant (13).

Occupational Hazards

Diclectin® may have a minor to moderate influence on the ability to drive and use machines. Because of potential drowsiness, Diclectin® should be prescribed with caution for patients who must drive automobiles or operate machinery.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reaction associated with doxylamine succinate is drowsiness. Other adverse drug reactions associated with doxylamine succinate may include: vertigo, nervousness, epigastric pain, headache, palpitation, diarrhea, disorientation, irritability, convulsions, urinary retention or insomnia.

Pyridoxine is a vitamin that is generally recognized as having no adverse effects.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In a randomized, double-blind, multi-center study in 2308 women with nausea and vomiting of pregnancy, various combinations of doxylamine succinate, dicyclomine hydrochloride and pyridoxine hydrochloride (each at 10 mg) were compared with placebo in an 8-way study design. The incidence of adverse reactions was 8.7% in the doxylamine/pyridoxine group versus 11.2% in the placebo group. In the doxylamine/pyridoxine group the most common adverse reactions were drowsiness (15/265, 5.7%), dizziness (3/265, 1.1%), fatigue or lethargy (2/265, 0.75%), gastric irritation, heartburn or indigestion (2/265, 0.75%) and headache (2/265, 0.75%). Corresponding values for the placebo group were drowsiness 8/269 (3%), dizziness 2/269 (0.75%), fatigue or lethargy 3/269 (1.1%), gastric irritation, heartburn or indigestion 0/269 (0%) and headache 4/269 (1.5%) (14).

In a double-blind comparison study of placebo and combination drug product (doxylamine succinate, dicyclomine hydrochloride and pyridoxine hydrochloride) in 81 patients 18 adverse events were reported (22.2%). In the active group 12 side effects were reported (29.2%) versus 6 (15%) in the placebo group. Feelings of weakness were reported by 2/41 (5%) in the active group versus 0% in the placebo group, tiredness by 2/41 (5%) in the active versus 2/40 (5%) in the placebo group and drowsiness by 3/41 (7%) in the active versus 1/40 (2.5%) in the placebo group. Also reported were: lack of energy, constipation, furry sensation in mouth, wind and headache (15).

Atanackovic et al., 2001 (8) evaluated the safety of higher than standard doses of Diclectin® in 225 pregnant women with nausea and vomiting of pregnancy in an observational, prospective study. A total of 123 women received standard doses of up to 4 tablets a day and 102 women received a higher than standard dose ("supradose") of 5 to 12 tablets/day. Despite a twice larger mean maximal dose of Diclectin®, women receiving the supradose did not report more prevalent adverse effects of Diclectin®. In the supradose group,

32% (31/97) reported sleepiness, tiredness and/or drowsiness compared with 35% (42/122) among the standard dose recipients. There was no association between the dose per kg and rates of reported maternal adverse effects with doses ranging from 0.1 mg/kg to 2.0 mg/kg (1-12 tablets).

Abnormal Hematologic and Clinical Chemistry Findings
None reported.

DRUG INTERACTIONS

Overview
No formal drug-drug interaction studies have been performed with Diclectin®.

Drug-Drug Interactions

Table 2 - Theoretical Drug-Drug Interactions for Doxylamine Succinate

Drugs	Effect	Clinical comment
MAOIs	Enhance	MAOIs may prolong and intensify the effects of doxylamine succinate (16).
Antimuscarinic Drugs	Additive	There is an increased risk of antimuscarinic side effects when doxylamine is given with other antimuscarinic drugs (17).
Alcohol and CNS depressants (barbiturates, hypnotics, narcotic analgesics, tranquilizers and sedatives)	Additive	Doxylamine succinate may increase the CNS-depressant effects (16).

Table 3 - Theoretical Drug-Drug Interactions for Pyridoxine Hydrochloride

Drugs	Effect	Clinical comment
Levodopa	Reduces effectiveness	Pyridoxine enhances peripheral decarboxylation of levodopa reducing the effectiveness of levodopa (16).

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
Two (2) Diclectin® delayed release tablets at bedtime to control nausea and vomiting occurring in the morning; additionally one (1) delayed release tablet in the morning and one (1) delayed release tablet mid-afternoon to control symptoms throughout the day. The dosage schedule may be individualized according to timing, duration, severity and frequency of the symptoms experienced by the patient. Diclectin® can be prescribed in any trimester of pregnancy.

Diclectin® is a delayed-release formulation that works optimally when given 4 to 6 hours prior to anticipated onset of symptoms. The delay in action may be prolonged when tablets are taken with food.

Diclectin® tablets being of a delayed release formulation should not be prescribed on an as needed basis (p.r.n.). It is important that Diclectin® is taken daily for optimal effect.

A gradual tapering dose of Diclectin® is recommended at the time of discontinuation to prevent a sudden onset of symptoms.

Missed Dose

In the event that a dose is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped. The prescribed dosing schedule should be continued.

Administration

Diclectin® is to be taken orally. Diclectin® tablets are a delayed release formulation therefore they should not be crushed or split.

OVERDOSAGE

Diclectin® is delayed release therefore signs and symptoms of intoxication may not be apparent immediately.

For management of suspected drug overdose it is recommended that a poison control center be contacted.

Signs and symptoms of intoxication may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion and tachycardia. If treatment is needed, it consists of gastric lavage or activated charcoal, whole bowel irrigation and a symptomatic treatment (18).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Diclectin® (doxylamine succinate and pyridoxine hydrochloride) provides the action of two unrelated compounds. Doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B6) provide anti-nauseant and anti-emetic activity (14, 19-20). The delayed action of Diclectin® permits the nighttime dose to be effective in the morning hours, when the patient needs it most.

Pharmacokinetics

Table 4a - Diclectin's® Pharmacokinetic Parameters Under Fed and Fasted Conditions in Healthy Female Volunteers for Doxylamine/Pyridoxine/Pyridoxal/Pyridoxal 5'-phosphate (21)

Value	Doxylamine Mean ± SD N = 22		Pyridoxine Mean ± SD N = 9		Pyridoxal Mean ± SD N = 16		Pyridoxal 5'-phosphate Mean ± SD N = 20	
	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted
AUC_{0-t} (ng.h/mL)	1567.23 ± 366.04	1519 ± 428.99	N/A	N/A	118.51 ± 55.09	107.76 ± 62.96	1191.69 ± 924.39	988.19± 685.40
$AUC_{0-\infty}$ (ng.h/mL)	1611.35 ± 372.16	1561.11 ± 429.78	N/A	N/A	N/A	N/A	2462.79 ± 1459.62	2997.77 ± 1793.78
C_{max} (ng/mL)	82.0 ± 15.5	85.9 ± 17.7	24.0± 14.0	55.1± 20.3	45.3 ± 16.3	61.4 ± 14.6	40.1 ± 10.4	32.5 ± 7.9
T_{max} (h)	10.6 ± 1.8	5.26 ± 1.55	7.67 ± 1.73	2.81± 1.13	9.38± 1.76	3.76 ± 0.88	12.7 ± 5.9	12.1 ± 9.1
Kel (h^{-1})	0.0593 ± 0.0098	0.0613 ± 0.0111	N/A	N/A	N/A	N/A	0.0215 ± 0.0090	0.0136 ± 0.0083
$T_{1/2el}$ (h)	11.98 ± 1.91	11.69 ± 2.33	N/A	N/A	N/A	N/A	36.40 ± 12.58	71.90 ± 46.52

Table 4b - Diclectin's® Pharmacokinetic Parameters Under Fed and Fasted Conditions in Healthy Female Volunteers for Total Pyridoxine (21)

Value	Total Pyridoxine* Mean ± SD N=20	
	Fed	Fasted
AUC_{0-t} (pmol.h/mL)	6257.73±3899.06	5224.88 ± 2983.11
$AUC_{0-\infty}$ (pmol.h/mL)	12189.53 ± 7389.52	12199.21 ± 6764.15
C_{max} (pmol/mL)	533 ± 201	695 ± 183
T_{max} (h)	8.91± 1.78	3.45 ± 1.11
Kel (h^{-1})	0.0312± 0.0221	0.0313 ± 0.0299
$T_{1/2el}$ (h)	36.67 ± 21.77	49.71 ± 42.52

* Total pyridoxine includes pyridoxine, pyridoxal, pyridoxal 5'-phosphate.

Absorption, Distribution, Metabolism and Excretion:

Diclectin®:
A randomized open-label, 2-way crossover relative bioavailability study in 22 healthy adult females compared the pharmacokinetics after a single dose of two (2 x [10 mg + 10 mg]) Diclectin® tablets under fed and fasted conditions. The administration of food delayed the absorption of both doxylamine and pyridoxine by approximately 5 hours. However, this delay did not affect the peak concentration or extent of absorption of doxylamine, as both the C_{max} and AUC were not distinguishable between treatments. In contrast, the peak concentration and extent of absorption of pyridoxine were considerably reduced when administered with food. The effect of food on the pyridoxine component is more complex, in that pyridoxine, pyridoxal and pyridoxal 5'-phosphate, also contribute to the biological activity. Although pyridoxal peak concentrations are somewhat reduced, pyridoxal 5'-phosphate peak concentrations are slightly increased and AUC values for both pyridoxal and pyridoxal 5'-phosphate are not affected by administration under fed conditions. Total pyridoxine mean peak concentrations are slightly reduced but extent of absorption, as measured by AUC, is unaffected by treatment (21).

Pyridoxine hydrochloride:
Pyridoxine is readily absorbed in the gastrointestinal tract, mainly in the jejunum. Pyridoxine is primarily metabolized in the liver; following phosphorylation, its main active metabolite, pyridoxal 5'-phosphate, is released into the circulation (accounting for at least 60% of circulating vitamin B6) and is highly protein bound; primarily to albumin. The metabolic scheme for pyridoxine is complex, with formation of primary and secondary metabolites along with interconversion back to pyridoxine. These metabolites including pyridoxal, have biologic activity. The major metabolite 4-pyridoxic acid, is inactive and is excreted in urine (22-26).

Doxylamine succinate:
Doxylamine is biotransformed in the liver by N-dealkylation to its principle metabolites N-desmethyl and N, N-didesmethyldoxylamine, which are excreted by the kidney (27).

Doxylamine can cross the blood-brain barrier and has a high affinity for H1 receptors in the brain (22).

Special Populations and Conditions

Race: No data is available on differences in the pharmacokinetics of either doxylamine succinate or pyridoxine hydrochloride in different races.

Hepatic Insufficiency: No data is available on differences in the pharmacokinetics of doxylamine succinate or pyridoxine hydrochloride in patients with hepatic insufficiency.

Renal Insufficiency: No data is available on differences in the pharmacokinetics of doxylamine succinate in renal insufficiency. For pyridoxine hydrochloride some metabolites are excreted renally (28). There are no data to suggest that this should alter the current dosage recommendation of Diclectin®.

Genetic Polymorphism: No data is available.

STORAGE AND STABILITY

Store at room temperature (15 to 30°C).

Protect from light.

Keep out of reach of children.

SPECIAL HANDLING INSTRUCTIONS

No special handling instructions are required.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each round, white, film-coated, delayed release tablet contains: doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg.

Nonmedicinal ingredients are as follows: ammonium hydroxide, n-butyl-alcohol, carnauba wax powder, colloidal silicon dioxide, croscarmellose sodium, D&C Red#27, denatured alcohol, FD&C Blue#2, hypromellose, isopropyl alcohol, magnesium stearate, magnesium trisilicate, methacrylic acid copolymer, microcrystalline cellulose 102, PEG 400, PEG 8000, polysorbate 80, propylene glycol, shellac glaze, simethicone, talc, titanium dioxide.

Tablets are imprinted with the pink image of a pregnant woman  . Bottles of 100.

The indicia serves as a method to diminish the incidence of erroneous ingestion by pregnant women or erroneous dispensing by pharmacists of therapeutic agents not prescribed or labeled for pregnant women (29-30). Noncompliance in the use of prescription medications is common among pregnant women owing to fear over fetal exposure and safety even in the case of drugs with appropriate safety data (31).

An observational, prospective cross-sectional study was conducted by the manufacturer to determine the teratogenic risk perception of pregnant women when viewing a plain white tablet and a white tablet imprinted with the image of a pregnant woman. The difference in teratogenic risk perception was highly significant ($p<0.0001$). In the survey group of 132 pregnant women the mean perception of teratogenic risk was decreased by 23.4% when viewing tablets imprinted with the image of a pregnant woman (32). By reducing the perception of teratogenic risk by pregnant women the pregnancy indicia may increase patient compliance and thus the effectiveness of Diclectin®.

DISEASE MANAGEMENT AND DICLECTIN® SURVEILLANCE PROGRAMS

Since 1996, the Motherisk* Program at the Hospital for Sick Children has maintained a toll-free bilingual (French-English) Nausea and Vomiting of Pregnancy (NVP) Helpline (1-800-436-8477) with the ongoing support of Duchesnay Inc. This service is available to women and healthcare professionals that would like to discuss the impact and management of NVP. Early recognition and treatment can prevent the progression of NVP to hyperemesis gravidarum and maternal and fetal complications. (7, 9, 33, 34)

Further to being a disease management line the NVP Helpline is acting as a surveillance program for Diclectin®. This service provides continuous monitoring of adverse events and the safe use of Diclectin® during pregnancy while generating valuable research data.

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* Motherisk
Hospital for Sick Children
555 University Ave.
Toronto, ON (M5G 1X8)
www.motherisk.org
1-800-436-8477

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

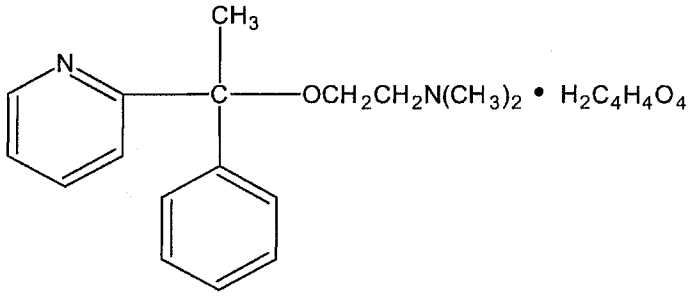
Drug Substance

Proper name: doxylamine succinate

Chemical name: Ethanamine, N,N-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1)2-[α-[2-(dimethylamino)ethoxy]-α-methylbenzyl] pyridine succinate (1:1)

Molecular formula and molecular mass: $C_{17}H_{22}N_2O \cdot C_4H_6O_4$
388.46

Structural formula:



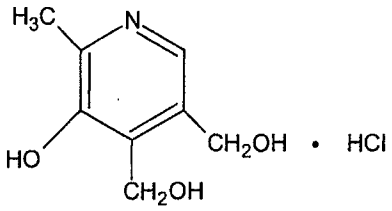
Physicochemical properties: Doxylamine succinate is very soluble in water and alcohol, readily soluble in chloroform and slightly soluble in ether and benzene.

Proper name: pyridoxine hydrochloride

Chemical name: 5-hydroxy-6-methyl-3,4-pyridine dimethanol hydrochloride

Molecular formula and molecular mass: $C_8H_{11}NO_3 \cdot HCl$
205.64

Structural formula:



Physicochemical properties: Pyridoxine hydrochloride is readily soluble in water, slightly soluble in alcohol and insoluble in ether.

CLINICAL TRIALS

Study demographics and trial design

Three double-blind, placebo-controlled studies support the efficacy of the combination of doxylamine succinate and pyridoxine hydrochloride in nausea and vomiting of pregnancy.

Table 5 - Summary of Patient Demographics for Double-blind, Placebo-controlled Clinical Trials in Nausea and Vomiting of Pregnancy

Study #	Trial design	Dosage, route of administration and duration[a]	Study subjects (n=number)	Mean age (Range)
A (NDA -10-598, 1975) (14)	8-way, randomized, double-blind, placebo-controlled, multi-center	Dox/Dic/Pyr; Dox/Pyr; Dic/Dox; Dic/Pyr; Dox, Dic; Pyr; Placebo. Oral. 7 days. 2 tablets at bedtime for 7 nights and if necessary 1 additional tablet in mornings and midafternoons.	2308[b]	NA
B (Geiger, et al. 1959) (35)	Double blind, placebo controlled	Dox/Dic/Pyr vs placebo. Oral. 2 tablets upon retiring and if results not satisfactory within 2-3 days, 1 or 2 additional tablets during morning hours.	110 (53 active; 57 placebo)	(19-40 years)
C (McGuinness and Binns, 1971) (15)	Double blind, placebo controlled	Dox/Dic/Pyr vs placebo. Oral. 2 tablets at bedtime for 14 nights.	81 (41 active, 40 placebo)[c]	(16-39 years)

[a] Dox = doxylamine succinate 10 mg; Dic = dicyclomine hydrochloride 10 mg; Pyr = pyridoxine hydrochloride 10 mg.
[b] Pregnant women complaining of nausea and/or vomiting in the first trimester were included. 1599 were evaluable for efficacy.
[c] Pregnant women complaining of nausea or vomiting in the first trimester were included. No patient beyond 20th week was admitted to the trial.

Study results

Table 6 - Results of Study A (NDA 10-598) in Nausea and Vomiting of Pregnancy (14)

Primary Endpoints	Doxylamine Succinate + Pyridoxine Hydrochloride	Placebo
Physician's evaluation of effectiveness (% moderate to excellent)	78%	57% ($p < 0.01$)
Physician's evaluation of % improvement in nausea	75%	52% ($p < 0.01$)
Physician's evaluation of % improvement in vomiting	73%	66% ($p = 0.17$)
Patient's evaluation of % reduction- in daily hours nausea	64%	31% ($p < 0.01$)
Patient's evaluation of % with no vomiting on 5 or more treatment days	48%	28% ($p < 0.01$)

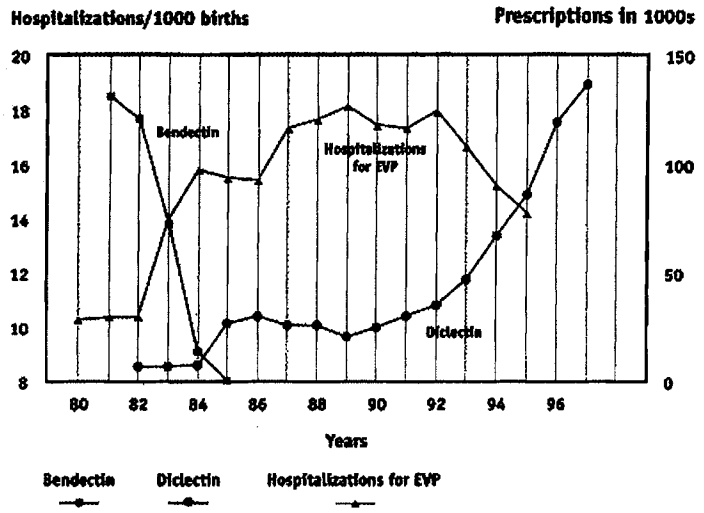
Table 7 - Results of Studies B and C in Nausea and Vomiting of Pregnancy (15, 35)

Study	Primary Endpoints	Doxylamine Succinate + Dicyclomine Hydrochloride + Pyridoxine Hydrochloride	Placebo
B (Geiger et al. 1959)	Relief from nausea and vomiting	94%	65% ($p<0.001$)
C (McGuinness and Binns, 1971)	Improvement in severity of nausea and vomiting of pregnancy	70.7%	55.0% ($p<0.05$)

A study was conducted to quantify rates of suboptimal use of pyridoxine hydrochloride-doxylamine succinate (Diclectin®); and to study responses to optimal doses of Diclectin® in women previously taking a suboptimal dose. Women who called the Motherisk NVP Helpline, and were taking only Diclectin® (pyridoxine hydrochloride and doxylamine succinate), were enrolled in the study and assessed for the severity of nausea and vomiting of pregnancy (NVP) with the Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system. A follow-up phone call occurred within 1 to 3 weeks after the intervention, at which time the overall PUQE score was repeated, along with individual scoring of symptoms of nausea, vomiting, and retching. Despite moderate to severe NVP, defined by the validated PUQE scoring system, most women (50/68) were receiving 2 tablets a day of Diclectin® instead of the recommended dose of 4 tablets a day. Their doses were subsequently increased according to body weight and individual symptoms. Following a mean doubling of the dose to 4 tablets a day, there was a significant decrease in length of nausea (from 4 to 3 hours, $p < 0.001$), frequency of vomiting (from mean 1.6 to 1.3 a day, $p = 0.02$), and overall PUQE score (from mean 7.5 to 6.1, $p < 0.001$) (36).

The effectiveness of this product for the treatment of NVP is illustrated in the inverse relationship between number of hospitalizations for excessive vomiting in pregnancy and number of prescriptions for Diclectin® in Canada. As prescriptions increase in number, hospitalizations for excessive vomiting in pregnancy decrease (22, 37).

FIGURE 1 - HOSPITALIZATIONS FOR EXCESSIVE VOMITING IN PREGNANCY (EVP) AND BENDECTIN/DICLECTIN® (COMBINATION OF 10 MG DOXYLAMINE SUCCINATE AND 10 MG PYRIDOXINE HYDROCHLORIDE) USE* IN CANADA



*Canadian Compuscript, 1981-1997. Quoted by permission.

Relative Bioavailability Studies

A randomized, 2-way crossover study of 18 healthy adult females investigated the absorption of doxylamine succinate and pyridoxine hydrochloride from Diclectin® tablets (2 x [10 mg + 10 mg]) versus an equivalent combination of reference doxylamine succinate and pyridoxine hydrochloride oral solutions (20 mL x 10 mg/10 mL), administered under fasting conditions. The pharmacokinetic parameters are presented in the table below. The delayed release properties of Diclectin® are evident in the different T_{max} values observed for both doxylamine, pyridoxine, pyridoxal and total pyridoxine between Diclectin® tablets and the corresponding solution. Values are 3 times higher for doxylamine, 6 times higher for pyridoxine, 4 times higher for pyridoxal and 6 times higher for total pyridoxine with the tablet formulation than for the oral solution. For pyridoxal 5'-phosphate, the T_{max} values were similar.

Peak plasma levels obtained with the oral solution are higher than those obtained with the delayed-release tablet formulation for pyridoxine, pyridoxal and total pyridoxine. This is expected as a delayed release tablet is being compared to an oral solution. Drugs in oral solution formulation are ready to be absorbed since the drug is already dissolved. Both the doxylamine and pyridoxine components of the delayed release tablets are fully absorbed compared to an equal dose administered as an oral solution (21).

Table 8 - Summary of Diclectin®'s Pharmacokinetic Parameters - Delayed Release Tablet Versus Solution (21)

Parameter	Doxylamine Geometric Mean Arithmetric Mean (CV%)		Pyridoxine Geometric Mean Arithmetric Mean (CV%)	
	Diclectin®	**Solution**	**Diclectin®**	**Solution**
AUC_{0-t} (ng•h/mL)	1611.93 1678.19 (32.69)	1560.91 1616.85 (28.38)	47.27 51.41 (45.17)	60.38 64.95 (41.48)
$AUC_{0-\infty}$ (ng•h/mL)	1658.66 1728.89 (33.04)	1602.06 1659.51 (28.30)	55.48 59.34 (37.66)	61.69 66.37 (39.71)
C_{max} (ng/mL)	89.5 90.4 (14.45)	97.2 98.7 (18.3)	44.5 50.7 (61.12)	87.4 96.5 (48.35)
T_{max} (h)	6.10 (28.99)	2.04 (41.62)	3.81 (31.40)	0.618 (29.04)
$T_{1/2\ el}$ (h)	11.76 (28.93)	11.91 (25.46)	0.34 (44.52)	0.26 (25.65)
Parameter	**Pyridoxal Geometric Mean Arithmetric Mean (CV%)**		**Pyridoxal 5'-Phosphate Geometric Mean Arithmetric Mean (CV%)**	
	Diclectin®	**Solution**	**Diclectin®**	**Solution**
AUC_{0-t} (ng•h/mL)	114.50 124.02 (37.65)	142.11 149.72 (33.52)	1300.32 1678.90 (73.75)	1236.61 1600.38 (80.33)
$AUC_{0-\infty}$ (ngoh/mL)	163.15 175.86 (34.61)	178.25 188.53 (35.27)	2998.54 3094.17 (31.94)	2926.95 3451.65 (61.71)
C_{max} (ng/mL)	59.4 62.3 (30.72)	80.2 82.8 (25.65)	40.5 42.9 (40.86)	39.6 41.6 (34.97)
T_{max} (h)	4.84 (29.75)	1.15 (22.49)	8.59 (32.28)	7.64 (50.82)
$T_{1/2\ el}$ (h)	1.51 (56.22)	1.27 (46.14)	55.64 (44.13)	59.05 (53.80)
Parameter	**Total Pyridoxine* Geometric Mean Arithmetric Mean (CV%)**			
	Diclectin®	**Solution**		
AUC_{0-t} (pmol•h/mL)	6712.85 8027.65 (64.48)	6475.51 7815.21 (70.32)		
$AUC_{0-\infty}$ (pmol•h/mL)	12828.78 14234.92 (51.24)	13850.42 15886.49 (56.66)		
C_{max} (pmol/mL)	684 709 (28.57)	994 1039.61 (32.33)		
T_{max} (h)	4.50 (33.65)	0.764 (36.33)		
$T_{1/2\ el}$ (h)	48.25 (50.35)	58.33 (49.73)		

*Total pyridoxine includes pyridoxine, pyridoxal, pyridoxal 5'-phosphate

DETAILED PHARMACOLOGY

Pharmacokinetics :

Table 9a - Diclectin's® Pharmacokinetic Parameters Under Fed and Fasted Conditions in Healthy Female Volunteers for Doxylamine/Pyridoxine/Pyridoxal/Pyridoxal 5'-phosphate (21)

Parameter	Doxylamine Mean ± SD N = 22		Pyridoxine Mean ± SD N = 9		Pyridoxal Mean ± SD N = 16		Pyridoxal 5'-phosphate Mean ± SD N = 20	
	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted
AUC_{0-t} (ng.h/mL)	1567.23 ± 366.04	1519 ± 428.99	N/A	N/A	118.51 ± 55.09	107.76 ± 62.96	1191.69 ± 924.39	988.19 ± 685.40
$AUC_{0-\infty}$ (ng.h/mL)	1611.35 ± 372.16	1561.11 ± 429.78	N/A	N/A	N/A	N/A	2462.79 ± 1459.62	2997.77 ± 1793.78
C_{max} (ng/mL)	82.0 ± 15.5	85.9 ± 17.7	24.0 ± 14.0	55.1 ± 20.3	45.3 ± 16.3	61.4 ± 14.6	40.1 ± 10.4	32.5 ± 7.9
T_{max} (h)	10.6 ± 1.8	5.26 ± 1.55	7.67 ± 1.73	2.81 ± 1.13	9.38 ± 1.76	3.76 ± 0.88	12.7 ± 5.9	12.1 ± 9.1
Kel (h^{-1})	0.0593 ± 0.0098	0.0613 ± 0.0111	N/A	N/A	N/A	N/A	0.0215 ± 0.0090	0.0136 ± 0.0083
$T_{1/2el}$ (h)	11.98 ± 1.91	11.69 ± 2.33	N/A	N/A	N/A	N/A	36.40 ± 12.58	71.90 ± 46.52

Table 9b - Diclectin's® Pharmacokinetic Parameters Under Fed and Fasted Conditions in Healthy Female Volunteers for Total Pyridoxine (21)

Parameter	Total Pyridoxine* Mean ± SD N=20	
	Fed	Fasted
AUC_{0-t} (pmol.h/mL)	6257.73 ±3899.06	5224.88 ± 2983.11
$AUC_{0-\infty}$ (pmol.h/mL)	12189.53 ± 7389.52	12199.21 ± 6764.15
C_{max} (pmol/mL)	533 ± 201	695 ± 183
T_{max} (h)	8.91 ± 1.78	3.45 ± 1.11
Kel (h^{-1})	0.0312 ± 0.0221	0.0313 ± 0.0299
$T_{1/2el}$ (h)	36.67 ± 21.77	49.71 ± 42.52

* Total pyridoxine includes pyridoxine, pyridoxal, pyridoxal 5'-phosphate.

A randomized open-label, 2-way crossover relative bioavailability study in 22 healthy adult females compared the pharmacokinetics after a single dose of two (2 x [10 mg + 10 mg]) Diclectin® tablets under fed and fasted conditions. The administration of food delayed the absorption of both doxylamine and pyridoxine by approximately 5 hours. However, this delay did not affect the peak concentration or extent of absorption of doxylamine, as both the C_{max} and AUC were not distinguishable between treatments. In contrast, the peak concentration and extent of absorption of pyridoxine were considerably reduced when administered with food. The effect of food on the pyridoxine component is more complex, in that pyridoxine, pyridoxal and pyridoxal 5'-phosphate, also contribute to the biological activity. Although pyridoxal peak concentrations are somewhat reduced, pyridoxal 5'-phosphate peak concentrations are slightly increased and AUC values for both pyridoxal and pyridoxal 5'-phosphate are not affected by administration under fed conditions. Total pyridoxine mean peak concentrations are slightly reduced but extent of absorption, as measured by AUC, is unaffected by treatment (21).

TOXICOLOGY

Reproductive Toxicology

Tyl et al., (38) studied a drug product containing equal concentrations of doxylamine succinate and pyridoxine hydrochloride in rats at doses of 0, 200, 500 and 800 mg/kg/day. Both maternal and fetal toxicity were evident at the two highest doses. Developmental toxicity included reduced prenatal viability and reduced fetal body weight per litter (500 and 800 mg/kg/day). No teratogenic effects of this drug were found even at the maternally toxic dose of 800 mg/kg/d, which is approximately 1000 times higher than the usual human dose. The finding of minor skeletal variations, such as a shortened 13th rib, only at the toxic high doses is consistent with general toxicity.

Teratology studies in rabbits and reproduction studies in rats were conducted with doxylamine succinate alone, dicyclomine HCl alone, and a drug product containing a combination of doxylamine succinate, dicyclomine HCl and pyridoxine HCl (39). One of three groups of rats received 3-60 mg/kg/day (5-90 times the Maximum Recommended Human Dose [MRHD]) of the combination, while the two other groups received 10-100 mg/kg/day (15-150 times the MRHD) of either dicyclomine or doxylamine. In the three rabbit groups, 3-30 mg/kg/day (5-45 times the MRHD) of the drug product containing the combination, and 10-100 mg/kg/day (15-150 times the MRHD) of either dicyclomine HCl or doxylamine succinate were given. No increase in congenital malformations or other adverse effects were noted in pregnancy when compared to nonexposed controls. None of these materials appeared to have any deleterious effects on reproductive parameters such as pregnancy maintenance, litter size, or fetal weight in the rabbit, except when toxic (100 mg/kg/day doxylamine succinate or dicyclomine HCl) levels were reached. In rats, these same drugs produced no alteration in breeding, conception, pregnancy maintenance, litter size, or fetal weight, although a mild dose-related decrease in neonatal weight gains occurred in pups from doxylamine succinate and dicyclomine hydrochloride-treated dams.

In the first part of his investigation, Hendrickx et al. (40), evaluated embryotoxicity of a combination of doxylamine succinate and pyridoxine hydrochloride in an uncontrolled small-scale study in preterm and term cynomolgus monkeys, rhesus monkeys and baboons. Some baboons received doxylamine succinate alone as opposed to the combination. Drugs were administered throughout the major period of organogenesis (gestation day 22 to 50). Cynomolgus and rhesus monkeys were given doses 10-40 times the MRHD, while baboons received doses of 1-10 times the MRHD or 10 times the MRHD for the group receiving doxylamine succinate only. A few cynomolgous monkeys received the combination product at doses 20 times the MRHD for 4 consecutive days. In these teratogenicity studies in the 3 species the treatment related effects of exposure to the combination of doxylamine succinate and pyridoxine hydrochloride in utero appear to be limited to a delay in closure of the ventricular septum that was evident at 100 days of gestation but not at term. Ventricular septal defects (VSD) were observed in 6 (40%) of the preterm cynomolgus monkeys, 2 (18%) of the preterm rhesus monkeys and 3 (23%) of the preterm baboons examined prenatally (day 100 of gestation). No dose response was evident and there were no other cardiac or extracardiac defects found except for one baboon fetus with multiple defects. No defects were observed in cynomolgus monkeys who were administered the combination of doxylamine succinate and pyridoxine hydrochloride for 4-day periods between 22 and 41 days of gestation. There was no association of this combination treatment with any noncardiac defect. In monkeys examined at term, there was no incidence of VSD, but one cynomolgous monkey had a mitral valve defect. This suggests an intrauterine delay in closure of the ventricular septum in monkeys, but that closure would occur before birth.

The second part of this investigation examined the embryotoxic and teratogenic potential of doxylamine succinate and pyridoxine hydrochloride in term cynomolgus monkeys. The combination of doxylamine succinate and pyridoxine hydrochloride pulverized tablets or placebo were administered double-blind by nasogastric intubation on days 22-50 of gestation at doses approximately 2, 5 and 20 times the MRHD. Fetuses were delivered by caesarean section near term and were examined. No congenital malformations were noted, and no evidence of embryo, fetal or maternal toxicity was observed (41).

Carcinogenicity

Two-year carcinogenicity studies in rats and mice were conducted at the U.S. National Center for Toxicological Research (NCTR). The rodents were administered doxylamine succinate at dose levels of 0, 500, 1000 and 2000 parts per million (ppm) in rats and dose levels of 0, 190, 375 and 750 ppm in mice. There were no increases in neoplastic lesions in female rats. Liver neoplasms in male rats were found only in the high-dose group. A trend test was significant ($p = 0.05$) for increased incidence of hepatocellular adenoma and carcinoma with increasing doses of doxylamine succinate, but the increased incidence of either lesion alone in the high dose group was not significant compared with controls. The incidence of these lesions was within the range historically observed in this strain of rats, and the results are not considered to have clinical relevance in humans.

In the mouse bioassay, tumors that showed a statistically significant increase versus the control group in a trend test and in pairwise comparisons included hepatocellular adenomas and thyroid follicular cell adenomas. Doxylamine succinate produced a significant increase in hepatocellular adenomas in the mid to high dose group in male mice and the high dose group in female mice. There was no increase in the incidence of hepatocellular carcinomas in male mice and no hepatocellular carcinomas observed in any female mice. Thyroid follicular cell adenomas also were increased in treated mice of both sexes. These observations are consistent with a hormonal imbalance caused by induction of cytochrome P450 by doxylamine succinate in mice. Since enzyme induction is not observed in humans (42), doxylamine succinate is not considered to pose a carcinogenic risk under clinical use (43).

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PART III: CONSUMER INFORMATION

DICLECTIN®
Doxylamine succinate, pyridoxine hydrochloride delayed release tablets (10 mg/10mg)

This leaflet is part III of a three-part "Product Monograph" published when Diclectin® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Diclectin®. It does not take the place of talking to your doctor, pharmacist or healthcare professional. Contact your doctor, pharmacist or healthcare professional if you have any questions about the drug. Keep this leaflet with the medicine. You may need to read it again. As Diclectin® is a prescription medicine, it should only be used under medical supervision.

ABOUT THIS MEDICATION

What the medication is used for:
The treatment of nausea and vomiting of pregnancy at any trimester of pregnancy.

What it does:
Diclectin® provides the anti-nauseant and anti-vomiting action of two different ingredients: doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B6).

When it should not be used:
You should not be given Diclectin® if you are allergic to any of the ingredients of Diclectin®.

What the medicinal ingredients are:
The medicinal ingredients of Diclectin® are doxylamine succinate (an antihistimine) and pyridoxine hydrochloride (vitamin B6).

What the important nonmedicinal ingredients are:
Nonmedicinal ingredients are as follows: ammonium hydroxide, n-butyl-alcohol, carnauba wax powder, colloidal silicon dioxide, croscarmellose sodium, D&C Red#27, denatured alcohol, FD&C Blue#2, hypromellose, isopropyl alcohol, magnesium stearate, magnesium trisilicate, methacrylic acid copolymer, microcrystalline cellulose 102 , PEG 400, PEG 8000, polysorbate 80, propylene glycol, shellac glaze, simethicone, talc, titanium dioxide.

This product does not contain gluten, tartrazine, sulfite or lactose.

What dosage forms it comes in:
Diclectin® is supplied in the form of a delayed release tablet, 10 mg doxylamine succinate + 10 mg pyridoxine hydrochloride. Each tablet is imprinted with a pink image of a pregnant woman. 

WARNINGS AND PRECAUTIONS

Diclectin® may cause drowsiness. Until you know how you will react to this medication do not drive or operate machinery.

INTERACTIONS WITH THIS MEDICATION

Deeper drowsiness could be produced if Diclectin® is taken in combination with alcohol or other drugs such as drugs for cough or colds, pain killers or sleep aids.

PROPER USE OF THIS MEDICATION

Usual dose:
Diclectin® should be taken as prescribed by your doctor or healthcare professional. Take two (2) Diclectin® delayed release tablets at bedtime to control nausea and vomiting occurring in the morning; additionally one (1) delayed release tablet in the morning and one (1) delayed release tablet mid-afternoon to control symptoms throughout the day. Your doctor or healthcare professional may adjust the dosing schedule according to your condition.

Diclectin® is a delayed-release formulation that works best when taken 4 to 6 hours before needed and should be taken on a daily basis. The delay in action may be prolonged when tablets are taken with food.

Do not stop taking Diclectin® on your own. Always consult your doctor or healthcare professional. They will gradually reduce your dose when stopping Diclectin® treatment to prevent a sudden return of nausea and vomiting symptoms.

This drug is specifically prescribed for you and your actual state of health. Do not give it to others, even if they have the same symptoms, and you yourself must not use it for any other condition than the one for which it was prescribed.

Tablets should not be crushed or split.

Overdose:
If you suspect an accidental overdose seek medical attention immediately. Do not wait for any signs or symptoms to appear before seeking medical attention.

Signs and symptoms of overdosage are restlessness, dryness of mouth, dilated pupils, sleepiness, dizziness, mental confusion and rapid heart beat.

Missed Dose:
If a dose of Diclectin® has been missed, take as soon as possible. However, if it is almost time for the next dose, skip the missed dose and continue with the regular dosing schedule. Do not double doses unless prescribed by your doctor or healthcare professional.

SIDE EFFECTS AND WHAT TO DO

Side effects: The most common side effect associated with Diclectin® is drowsiness. Other less common side effects might be dizziness, nervousness, stomach pain, headache irregular heart beat, diarrhea, disorientation, irritability, seizures, difficulty urinating or insomnia.

This is not a complete list of side effects.

For any unexpected effects while taking Diclectin® contact your doctor, pharmacist or healthcare professional.

HOW TO STORE IT

Store at room temperature (15-30°C).

Protect from light.

Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs . If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345
toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician, pharmacist or healthcare professional.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Duchesnay Inc. at:
2925 Boul. Industriel
Laval, Quebec, Canada
H7L 3W9
Tel: 1-888-666-0611
Fax: 1-888-588-8508

If you have any questions regarding the management or treatment of nausea and vomiting of pregnancy or wish to enroll in a Diclectin® Surveillance Program, please contact the Motherisk NVP Helpline (bilingual French-English) at the Toronto Hospital for Sick Children at:
1-800-436-8477

This leaflet was prepared by Duchesnay Inc.

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